Universidade Estadual Paulista “Júlio de Mesquita Filho”
Faculdade de Odontologia de Araçatuba (FOA – UNESP)
Programa de Pós-Graduação em Odontologia
Àrea de Concentração: Estomatologia e Psiconeuroimunologia

Bruna Amélia Moreira Sarafim da Silva

Atraso no diagnóstico do câncer: as razões podem começar na infância

Araçatuba – SP
2022

Bruna Amélia Moreira Sarafim da Silva

Atraso no diagnóstico do câncer: as razões podem começar na infância

Tese apresentada à Faculdade de Odontologia do Campus de Araçatuba – Universidade Estadual Paulista "Júlio de Mesquita Filho" – UNESP, para obtenção do Título de Doutor em Odontologia (Área de concentração em Estomatologia e Psiconeuroimunologia).

Orientador: Prof. Ass. Dr. Daniel Galera Bernabé

Araçatuba – SP
2022

Catalogação na Publicação (CIP)

Diretoria Técnica de Biblioteca e Documentação – FOA / UNESP

S586a

Silva, Bruna Amélia Moreira Sarafim da.
Atraso no diagnóstico do câncer: as razões podem começar na infância / Bruna Amélia Moreira Sarafim da Silva. - Araçatuba, 2022
42 f. : tab.

Tese (Doutorado) – Universidade Estadual Paulista, Faculdade de Odontologia de Araçatuba
Orientador: Prof. Daniel Galera Bernabé

1. Neoplasias 2. Trauma psicológico 3. Adultos sobreviventes de eventos adversos na infância 4. Neoplasias de cabeça e pescoço I.T.

Black D62
CDD 617.64

Ana Claudia M. Grieger Manzatti CRB-8/6315

ERRATA

Folha	Linha	Onde se lê	Leia-se
10	9	À Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP pelo financiamento e apoio designado ao projeto de pesquisa através da concessão de Auxílio Regular (Processo nº 2018/06927-2)	À Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP e Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES), Código de financiamento 001, pelo financiamento e apoio designado ao projeto de pesquisa através da concessão de bolsa de doutorado (Processo nº 2018/06927-2, Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)À Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP pelo financiamento e apoio designado ao projeto de pesquisa através da concessão de Auxílio Regular (Processo nº 2016/25255-0)

Dedicatória

Aos pacientes do Centro de Oncologia Bucal da Faculdade de Odontologia de Araçatuba – UNESP pela disposição e por compartilharem comigo suas dores e angústias. Serei eternamente grata por esta oportunidade. Dedico este estudo a cada um deles que se dispuseram a participar da pesquisa, agradeço pelas histórias contadas, as dores compartilhadas e os sorrisos divididos.

AGRADECIMENTOS

AGRADECIMENTOS

Ao meu orientador **Daniel Galera Bernabé**, por me incentivar a persistir sempre, por ter contribuído para o meu crescimento científico, e principalmente, por respeitar minhas limitações. Sou grata pela amizade, confiança, pela oportunidade de fazer parte de sua equipe e por ser o maior incentivador na superação de meus limites. Sua perseverança e constante foco nos seus ideais sempre foram uma inspiração para que eu fizesse o mesmo. Finalmente, agradeço por me estimular a ter a visão crítica e questionadora sobre a vida.

À **Banca Examinadora** por aceitarem avaliar meu trabalho. Agradeço imensamente por cada um poder fazer parte de um momento tão importante para mim.

Ao professor **Glauco Issamu Miyahara**, por me aceitar como psicóloga voluntária no Centro de Oncologia Bucal, por ser um grande incentivador para que eu concluísse a pós-graduação. Sempre me auxiliou no que precisei, me dando orientações nas dificuldades que tive e me estimulando a continuar persistindo.

Ao professor **José Eduardo Corrente**, por todo o apoio, auxílio e parceria nas análises estatísticas deste e de outros trabalhos. Sou imensamente grata por tudo.

Ao professor **Éder Ricardo Biasoli**, pela colaboração e contribuição para o meu crescimento acadêmico e por me auxiliar a entender a linguagem médica dos prontuários.

À psicóloga **Gabrielle Dias Duarte**, pela amizade, confiança, confidencialidade e parceria em todos os meus momentos. Sempre que precisei, você estava por perto. Agradeço imensamente sua amizade, vou leva-la comigo para sempre.

À fonoaudióloga **Daniene Tesoni Cassavara Ribeiro**, pela parceria tanto no trabalho como fora, pela amizade e companheira de ideal. Obrigada pelo grande auxílio quanto à pesquisa e pela compreensão nos momentos mais difíceis da pós-graduação.

À fisioterapeuta **Regiane Mazzarioli Pereira Nogueira**, pela amizade, apoio em todos os momentos e por me inspirar a ser amorosa e dedicada com os pacientes.

À enfermeira **Anne Cristina de Faria Cocato**, pelo auxílio no recrutamento dos pacientes, pela paciência e apoio que sempre me deu. Sua dedicação com os pacientes sempre foi um grande estímulo para mim.

À Jane Fátima M. Fernandes da Silva e **Adriana de Paula e Silva Rahal Leal,** por sempre e em todos os momentos estarem dispostas a me auxiliar com os prontuários ou nos atendimentos com os pacientes. A dedicação ao trabalho e impecável organização de cada uma me inspira muito. Agradeço pelas nossas conversas e apoio que sempre me deram.

Ao **Vitor Boneti Valente**, um grande amigo e parceiro da pós-graduação, sempre esteve disposto a me ajudar no que precisei e por sempre ser alegre e positivo frente às dificuldades que enfrentamos.

À **Giseli Mitsuy Kayahara**, pelo grande companheirismo em todas as etapas da pós-graduação. Sua atenção e parceria foram muito importantes para mim. Levarei sua amizade para sempre comigo.

À **Daniela Brito Bastos**, pela parceria e por compartilhar suas dores e alegrias comigo. Sua confiança e amizade são muito importantes para mim. Conte sempre comigo.

À **Tamara Fernandes**, pelo apoio e companheirismo em todas as fases deste trabalho. Sua amizade e parceria são muito importantes para mim.
Aos meus pais **Felício e Cristina**, por serem meu porto seguro, me apoiarem sempre e estarem dispostos a me ouvir em qualquer instante. Amo vocês.

Às minhas irmãs **Natália** e **Carolina** e ao meu cunhado **Hamilton**, por sempre e sempre estarem ao meu lado, em todos os momentos de minha vida. Amo vocês.

À F**undação de Amparo à Pesquisa do Estado de São Paulo – FAPESP** pelo financiamento e apoio designado ao projeto de pesquisa através da concessão de Auxílio Regular (Processo nº 2018/06927-2)

Ao **João Batista Munhoz Costa**, meu amor e confidente. Agradeço por todos os momentos que passamos juntos, amadurecemos juntos, compartilhamos nossas vidas e esses são os meus melhores momentos.

Aos **pacientes do COB**, que aceitaram participar deste estudo, pois nada disso seria possível sem a colaboração de cada um deles. Serei eternamente grata pela oportunidade que tive no doutorado.

Á **Faculdade de Odontologia de Araçatuba (FOA)**, por abranger seus métodos de ensino para outras áreas.

Epígrafe

"Um dia quando olhares para trás, verás que os dias mais belos foram aqueles em que lutastes. Só a experiência própria é capaz de tornar sábio o ser humano".

Sigmund Freud

Silva BAMS. Atraso no diagnóstico do câncer: as razões podem começar na infância [tese]. Araçatuba: Faculdade de Odontologia da Universidade Estadual Paulista; 2022.

RESUMO

A demora no diagnóstico do câncer atrasa o início do tratamento e tem impacto adverso no prognóstico do paciente. Embora o trauma infantil seja uma realidade comum na vida dos indivíduos, a ciência de sua ocorrência e consequências ainda são negligenciados em portadores de doenças crônicas. Estudos de nossa equipe e outros têm mostrado evidências das consequências do trauma infantil sobre aspectos emocionais, comportamentais e clinicopatológicos em pacientes com câncer. No entanto, até o momento, não há estudos que avaliaram a associação do trauma na infância com o atraso para o diagnóstico do câncer. O objetivo da presente pesquisa foi avaliar, pela primeira vez, a relação entre a ocorrência de trauma infantil e o tempo de demora para o diagnóstico da doença em um grupo de pacientes com câncer de cabeça e pescoço (CCP). Neste estudo transversal, 111 pacientes com câncer de cabeça e pescoço foram avaliados quanto aos fatores preditores para o tempo prolongado do paciente procurar atendimento e de sua trajetória no sistema de saúde até o diagnóstico da doença. O ponto de corte para avaliação do atraso para o diagnóstico foi de 3 meses, considerando até 3 meses como menor atraso e mais de 3 meses como maior atraso. Dados demográficos, clinicopatológicos e comportamentais foram extraídos dos prontuários dos pacientes. O Questionário sobre Trauma na Infância (QUESI) foi utilizado para avaliar a ocorrência de trauma infantil. Análises de regressão múltipla foram usadas para avaliar a associação das variáveis demográficas, comportamentais e clinicopatológicas, bem como da ocorrência de trauma na Infância com tempo de demora para o diagnóstico de câncer. Os resultados mostraram que o tempo médio de demora para os pacientes com CCP procurarem atendimento após perceber o primeiro sinal da doença foi de 129,50 dias, e o tempo médio de atraso entre o paciente procurar o primeiro serviço de saúde após perceber o tumor e receber o diagnóstico definitivo de câncer foi 196,43 dias. A ocorrência de abuso físico na infância foi uma variável independente para maior demora do paciente em procurar o primeiro atendimento após ter percebido o primeiro sintoma de câncer (OR = 3,22, IC = 1,020-10,183, p = 0,046). Pacientes que tinham o tumor localizado na laringe (OR = 13,5, IC = 2,645-69,355, p = 0,002) e tinham histórico de abuso emocional na infância (OR = 6,7, IC = 1,974-23,293, p = 0,002)

eram mais propensos a terem um tempo maior que 3 meses entre a primeira consulta em um serviço de saúde e o recebimento do diagnóstico de câncer. Pacientes do sexo feminino (OR = 5,6, IC = 1,658-18,934, p = 0,006) e com o tumor localizado na laringe (OR = 11,2, IC = 2,204-56,987, p = 0,004), tiveram um maior atraso entre perceber o primeiro sintoma e ter o diagnóstico da doença. Em conjunto a fatores clinicopatológicos, o histórico de experiências traumáticas na infância pode ser preditivo para um maior atraso do paciente com câncer procurar os serviços de saúde e receber o diagnóstico. Os resultados do presente estudo devem estimular que a redução do trauma no período infantil seja considerada no desenvolvimento de estratégias para a prevenção secundária do câncer.

Palavras-chave: Neoplasias. Trauma psicológico. Adultos sobreviventes de eventos adversos na infância. Neoplasias de cabeça e pescoço.

Silva BAMS. Delay in cancer diagnosis: the reasons may start in childhood. [thesis]. Araçatuba: UNESP - São Paulo State University; 2022.

ABSTRACT

Delay in the diagnosis of cancer retard the initiation of treatment and has an adverse impact on the patient's prognosis. Although childhood trauma is a common reality in the lives of individuals, the science of its occurrence and consequences are still neglected in patients with chronic diseases. Studies by our team and others have shown evidence of the consequences of childhood trauma on emotional, behavioral and clinicopathological aspects in cancer patients. However, to date, there are no studies that have evaluated the association of childhood trauma with delay in cancer diagnosis. The objective of the present research was to evaluate, for the first time, the relationship between the occurrence of childhood trauma and the delay time for the diagnosis of the disease in a group of patients with head and neck cancer (HNC). In this cross-sectional study, 111 patients with head and neck cancer were evaluated regarding predicting factors for the patient's prolonged time to seek care and their trajectory in the health system until the diagnosis of the disease. The cut-off point for evaluating the delay for diagnosis was 3 months, considering up to 3 months as the shortest delay and more than 3 months as the longest delay. Demographic, clinicopathological and behavioral data were extracted from the patients' records. The Childhood Trauma Questionnaire (CTQ) was used to assess the occurrence of childhood trauma. Multiple regression analyzes were used to assess the association of demographic, behavioral, and clinicopathological variables, as well as the occurrence of childhood trauma with time delay for the diagnosis of cancer. The results showed that the average delay for HNC patients to seek care after noticing the first sign of the disease was 129.50 days, and the average delay time between the patient seeking the first healthcare professional after noticing the tumor and receiving the definitive diagnosis of cancer was 196.43 days. The childhood physical abuse occurrence was an independent variable for the patient's longer delay in seeking first care after having noticed the first symptom of cancer (OR = 3.22, CI = 1.020-10.183, p = 0.046). Patients who had the tumor located in the larynx (OR = 13.5, CI = 2.645-69.355, p = 0.002) and had a history of childhood emotional abuse (OR = 6.7, CI = 1.974-23.293, p = 0.002) were more likely to have a time greater than 3 months between the first consultation at a health service and receiving the diagnosis of cancer.

Female patients (OR = 5.6, CI = 1.658-18.934, p = 0.006) and with the tumor located in the larynx (OR = 11.2, CI = 2.204-56.987, p = 0.004), had a longer delay between noticing the first symptom and being diagnosed with the disease. In conjunction with clinicopathological factors, the history of traumatic experiences in childhood may be predictive of a longer delay in the cancer patient seeking health services and receiving the diagnosis. The results of the present study should encourage the reduction of childhood trauma to be considered in the development of strategies for secondary cancer prevention.

Keywords: Neoplasms. Psychological trauma. Adult survivors of child adverse events. Head and neck neoplasms.

LISTAS

LISTA DE TABELAS

LISTA DE ABREVIATURAS

CCI Charlson Comorbidity Index

CTQ Childhood Trauma Questionnaire

CTS childhood trauma subtypes

HNC Head and Neck Cancer

HNSCC Head and Neck Squamous Cell Carcinoma

SCC squamous cell carcinoma

UICC International Union for Cancer Control

WHO World Health Organization

Sumário

SUMÁRIO

Delay in cancer diagnosis: the reasons may start in childhood[1]

Sarafim-Silva BAM[a], Duarte GD[a], Corrente JE[b], Biasoli ER[a], Miyahara GI[a], Bernabé DG[a*]

[a]Psychosomatic and Education Research Center, Oral Oncology Center, School of Dentistry, São Paulo State University - UNESP, 1193 José Bonifácio Street, Araçatuba, SP, Brazil

[b]*Research Support Office, Botucatu Medical School (UNESP), Botucatu, São Paulo, 18618-687, Brazil*

Conflict of Interest: The authors declare that they have no conflict of interest.

Keywords: Cancer, Squamous cell Carcinoma, Head Neck Cancer, Oral Cancer; Diagnosis, Cancer Diagnosis, Cancer Diagnosis Delay, Diagnosis Delay, Delay time, Childhood Trauma, Childhood Maltreatment, Childhood Adversity, Early Live Stress, Childhood Trauma Subtype.

Funding Support: This study was supported by the São Paulo State Research Foundation (FAPESP). FAPESP grant 2018/06927-2 supported Bruna A M Sarafim-Silva in her doctoral-degree research.

***Address correspondence and reprint requests to:**

Daniel Galera Bernabé.

Assistant Professor, Psychosomatic and Education Research Center, Oral Oncology Center, São Paulo State University (UNESP), School of Dentistry, Araçatuba, SP, Brazil, 1193 José Bonifácio St, Araçatuba, SP 15050-015, + 55 18 36363268 / 36363275 E-mail: daniel.bernabe@unesp.br

[1] Normalization according to the periodic New England Journal of Medicine (NEJM) (Anexo B)

1 INTRODUCTION

Unfortunately, a large number of cancer patients are still diagnosed with the disease at an advanced clinical stage.[1] If there is on maxim universally accepted in the context of oncology, it is that the prognosis of patients with an advanced clinical stage is worse compared to those patients diagnosed with the disease at an early stage.[1,2] In general, cancer prognostic parameters such as the level of invasion of the primary tumor and the occurrence of regional or distant metastases, are highly dependent on the time of disease evolution.[1-4] The delay in cancer diagnosis and treatment has an adverse impact on the patient's prognosis, increasing the chances of disease recurrence, with higher treatment cost and low survival.[2,3] Patients who delay longer to seek care after noticing the first sign or symptom of the tumor tend to be diagnosed with advanced-stage disease.[3] There is a consensus that delays by both the patient and the health system are the main factors associated with a worse prognosis.[1-4] The World Health Organization (WHO) intends target to reduce by one-third premature mortality from non-communicable diseases by 2030.[5] For this, it developed the program Comprehensive Cancer Control, with the goal to detect the disease early, consequently, increasing the chances of cure, improving the quality of life and well-being of the patient, decreasing the number of treatments and hospitalizations and increasing survival.[2]

The causes of delayed diagnosis of cancer have been widely explored, being low socioeconomic status and education, poor social support and lack of aware of the disease's symptoms the main factors related to longer patient delay.[1,4,6] In addition, the workload and family responsibilities are also common barriers that influence the patient's delay.[4] Women in particular blames their family obligations as one of the main causes for delaying their search for a health professional.[4] Another relevant point is the emotional repercussions triggered after the patient notices the first disease's symptoms. Some feelings like fear can be paralyzing, causing to the patient postpone seeking for a health professional instead of accelerating his appointment.[4] The delay related to the health system depends on two important factors.[1,7] The first is the professional's failure to detect malignant symptoms, often mistaken as signs of common illnesses.[1,7] An improper diagnosis may also considerably delay the initiation of cancer treatment.[1,7] The second factor is the long waiting time for making appointments, exams, and procedures necessary for diagnosis of the tumor.[7]

Childhood trauma is characterized by behaviors that pose a risk to the child's physical and/or emotional well-being.[8.9] The main subtypes of child maltreatment are physical, emotional and sexual abuse and physical and emotional neglect.[8,9] Abuse is defined by behaviors towards the child that go beyond the norms of conduct and/or behaviors that carry substantial risk of causing physical and emotional harm.[8,9] The negligence is conceptualized as the inability to meet the child's basic needs, in the physical and emotional spheres.[8,9] Over the past 10 years, studies have shown strong evidence of the consequences of childhood trauma on emotional, behavioral and clinicopathological factors in cancer patients.[10-12] Patients with a history of stressful events in the childhood period have high levels of anxiety, depression and worse psychological well-being after diagnosis and during cancer treatment.[10-12] High levels of depression have been associated with childhood physical, sexual and emotional neglect and abuse in patients with breast, colorectal, lung and head and neck cancer.[10-14] A previous study from our center showed that having suffered emotional neglect in childhood was a predictor for advanced clinical staging in head and neck squamous cell carcinoma (HNSCC) patients. However, the factors behind this association are still unknown.[12] In view of the previous findings, we hypothesized that childhood trauma may be a relevant behavioral modulating factor with a potential effect in delaying the diagnosis of cancer in later stages of life. Thus, in the present study, we used a sample of head and neck cancer (HNC) patients to investigate for the first time the relationship between the occurrence of trauma in childhood and the delay in the diagnosis of cancer.

2 METHODS

Ethical Statements

This study was approved by the human studies committee of the Araçatuba Dental School, São Paulo State University (UNESP). Informed consent was obtained from all participants.

Patients

The study included patients with a definitive diagnosis of head and neck cancer who were registered and treated in the Oral Oncology Center, Araçatuba Dental School, São Paulo State University (UNESP). Patients who completed the following criteria were included: histopathological diagnosis of squamous cell carcinoma (SCC); tumors located in the oral cavity, oropharynx or larynx. Patients who had previous diagnosis of cancer, under the age of 18 years, and those with cognitive deficit that could interfere with an understanding of the questionnaires were excluded.

Demographic, Clinicopathological and Behavioral Variables

Demographic (age, gender, marital status, family income, education, living with someone), clinicopathological (comorbidity, tumor location, T classification, regional metastasis, clinical staging) and behavioral data (cigarette and alcohol consumption) were obtained by the medical team at the patient's admission once the cancer diagnosis had been established. The clinical staging was defined on the basis of the UICC criteria.[15] The occurrence and severity of comorbidity was assessed according to the Charlson Comorbidity Index (CCI).[16,17] Tobacco and alcohol consumption was graded according to abstainers, light (up to 10 cigarettes and 1-2 doses, per day), moderate (11 to 20 cigarettes and 3-4 doses, per day), and heavy (over 20 cigarettes and more than 4 doses, per day).[12,18]

Childhood Trauma Measurement

Childhood trauma occurrence was assessed by the main investigator before starting cancer treatment using the Childhood Trauma Questionnaire (CTQ). The CTQ is an instrument that assesses abuse and neglect experienced in childhood.[19] The questionnaire was translated and validated into Portuguese in 2006 by Grassi-Oliveira, Stein e Pezzi.[20] The assessment is made following five criteria for traumatic events: physical abuse, emotional abuse, sexual abuse, physical neglect and emotional neglect.[19,20] The instrument is recommended for over 12 years of age and has a score of five points, being 1 (never), 2 (few), 3 (sometimes), 4 (many times) and 5 (always).[19,20]

Analysis of the Delay Time to Cancer Diagnosis.

The assessment of the delay time for HNSCC patients to seek care after noticing the first sign or symptom of the tumor was carried out through a semi-structured interview. This interview contains questions regarding the delay time the patient to seek the first assistance, and the number of professionals who attended the patient before the definitive diagnosis of the disease. The delay in cancer diagnosis was evaluated considering the patient's delay (period between the first perception of the first sign of the tumor and the search for a health professional), delay time in the health system (time between the patient's appointment with the first health professional and the definitive diagnosis of cancer), and the total delay time (period between the first perception of the disease and the diagnosis of cancer). All different delay times were evaluated in days.

Statistical Analysis

The SPSS program (SPSS, Inc., Chicago, IL) was used to perform univariate and multivariate analyses. The data were checked for normality, and Chi-Square Test and Fisher's Exact Test were used to investigate the association between the sociodemographic, biobehavioral, and clinicopathological variables, overall CTQ score and the five childhood trauma subtypes, with the three different delay types (patient's delay, health system delay and total delay) for the cancer diagnosis. Continuous

measures of CTQ were tested for normality using the Shapiro-Wilk test. The results showed asymmetry to the right, rejecting the hypothesis of normality ($p<0.0001$). The median was used as cut-off point. CTQ scores below or above the median were used to define lower or higher occurrence of trauma. Moreover, continuous CTQ data were also classified in quartiles 1 and 2 considering very low and low occurrence of childhood trauma, respectively, and quartiles 3 and 4 as high and very high occurrence, respectively. To analyze the childhood trauma subtypes (CTS) a binary measure was used to assess the occurrence or not of each CTS. Delay time measures in days were categorized as follows: patient and healthcare system delay times were divided into shorter delay for cancer diagnosis (up to 90 days) and longer delay (more than 90 days). The total time was divided into shorter delay (up to 180 days) and longer delay (more than 180 days). In the logistic regression analyses, two model were used to the study. In the first model the sociodemographic, clinicopathological, biobehavioral and CTQ variables were considered as independent variables, and the binary measure of the three delay times for cancer diagnosis as dependent variables. In the second model, all analyzes were adjusted for gender, age, marital status, income and education. The P values $<.05$ were considered significant for all analyses.

3 RESULTS

Epidemiological and Clinicopathological Characteristics of the HNSCC Patients

One hundred and eleven HNSCC patients met inclusion criteria, of whom 71 (64%) had tumors located in oral cavity, 28 (25.2%) in oropharynx and 12 (10.8%) in larynx (Table 1). Most of the patients were men (78.4%), of middle age (52.3%), married (56.8%). Only 18.9% lived alone, while 81.1% were residing with their partner and/or children. Fifty-four HNC patients (48.6%) reported low education (incomplete elementary school), followed by 34.2% with intermediary education (completed elementary school) and 17.1% with higher education (high school). The majority of the patients (57.7%) had low income, while 46.8% had at least one type of comorbidity (Table 1). As for the clinical staging, 54% of the HNC patients had the disease in an early stage (I and II), while 46% advanced stage (III and IV). Data regarding T classification, regional metastasis, CCI, and tobacco and alcohol consumption may be seen in Table 1. Most of the HNC patients (88.3%) had experienced at least one type of childhood trauma. The most common childhood trauma reported in CTQ was emotional neglect (34.2%) (Table 1), followed by physical child abuse (28.8%), physical child neglect (17.1%) and emotional child abuse (7.2%). Only one patient (0.9%) reported had suffered sexual abuse in childhood (Table 1).

Table 1. Demographic, clinicopathological and behavioral characteristics and CTQ measurements of patients with head and neck cancer

Variables	*N (%)*	*M*	*Med*
Sex			
Male	87 (78.4)		
Female	24 (21.6)		
Age range (years)			
0-45	11 (9.9)		
46-65	58 (52.3)		
> 65	42 (37.8)		
Marital status			
Not married	48 (43.2)		
Married	63 (56.8)		
Live alone			
No	90 (81.1)		
Yes	21 (18.9)		
Education			
Low education	54 (48.6)		
Intermediary education	38 (34.2)		
High education	19 (17.1)		
Income (R$/month)			
Low (until 1,000)	64 (57.7)		
Intermediary (1,100 – 5,000)	43 (38.7)		
High (> 5,000)	4 (3.6)		
Tumor location			
Oral Cavity	71 (64)		
Oropharynx	28 (25.2)		
Larynx	12 (10.8)		
T – classification			
T1	20 (18)		
T2	40 (36)		
T3	30 (27)		
T4	21 (19)		
Regional metastasis			
N0	80 (72.1)		
N+	31 (27.9)		
Clinical stage			
I	20 (18)		
II	34 (30.6)		
III	21 (18.9)		
IV	36 (32.4)		
CCI score*			
0	59 (53.2)		
1	35 (31.5)		
2	17 (15.3)		
Comorbidity type			
Hypertension	40 (76,9)		
Diabetes	10 (19.2)		
Others	2 (3,9)		
Smoking			
No	15 (13.5)		
Current smoker	70 (63.1)		

Ex-smoker	26 (23.4)		
Tobacco intensity			
Light	19 (19.8)		
Moderate	53 (55.2)		
Heavy	24 (25)		
Alcohol Consumption			
No	16 (14.4)		
Current drinker	58 (52.3)		
Ex-drinker	37 (33.3)		
Alcohol intensity			
Light	30 (31.5)		
Moderate	28 (29.4)		
Heavy	37 (39.1)		
Childhood Trauma			
No	13 (11.7)		
Yes	98 (88.3)		
Overall CTQ*		33.85	30
Quartile CTQ*			
1	34 (30.6)		
2	27 (24.3)		
3	23 (20.7)		
4	27 (24.3)		
Emotional neglect	38 (34.2)	8.30	6
Physical abuse	32 (28.8)	7.00	6
Physical neglect	19 (17.1)	7.03	5
Emotional abuse	8 (7.2)	6.43	5
Sexual abuse	1 (0.9)	5.09	5

*CCI: Charlson Comorbidity Index; **CTQ, Childhood Trauma Questionnaire; Values are mean (M) and median (Med).*

Delay in Cancer Diagnosis.

The average delay for HNC patients to seek care after noticing the first sign of the disease was 129.50 days (Table 2). The minimum time for a patient to seek care was 1 day, while the maximum time was 1825 days. Patients who had tumors located in the oral cavity delay an average of 139.08 days to look for a health professional after noticing the first symptom (Table 2). Patients with oropharyngeal cancer delay an average of 100.46 days, while patients with laryngeal cancer took an average time of 140.58 days (Table 2). The average delay time between the patient seeking the first healthcare professional after noticing the tumor and receiving the definitive diagnosis of cancer was 196.43 days. The minimum delay time was 7 days and the maximum time was 2465 days. In the group of patients with oral cancer, the average delay was 179.98 days (Table 2). In the group of oropharyngeal and laryngeal cancer patients, the mean times were 204.89 days and 274 days, respectively (Table 2). Finally, the total delay time for disease diagnosis of the HNC patients was 326.08 days, with a

minimum delay time of 20 days and a maximum delay time of 2555 days. Patients with oral cancer had a mean total delay time of 318.87 days, followed by 306.42 days for patients with oropharyngeal cancer and 414.58 days for patients with laryngeal cancer (Table 2).

Table 2. Delay in cancer diagnosis in HNC patients.

Variables	*N (%)*	*M*	*Med*
Patient delay time			
Total HNSC	111 (100)	129.50	60
Oral	71 (64)	139.08	60
Oropharynx	28 (25.2)	100.46	52.5
Larynx	12 (10.8)	140.58	45
Health system delay time			
Total HNSC	111 (100)	196.43	60
Oral	71 (64)	179.98	60
Oropharynx	28 (25.2)	204.89	60
Larynx	12 (10.8)	274	272.5
Total delay time			
Total HNSC	111 (100)	326.08	150
Oral	71 (64)	318.87	120
Oropharynx	28 (25.2)	306.42	150
Larynx	12 (10.8)	414.58	365

Values are mean (M) and median (Med).

Associations between the study variables and the differents delay types for cancer diagnosis.

Univariate analysis showed that the occurrence of childhood physical abuse subtype was associated with a longer delay time (more than 3 months) for the patient to seek care after noticing the first sign of the disease (p=0.030) (Table 3). Higher comorbidity index (p=0.030), smoking (p=0.003), low global occurrence of traumatic events in childhood (p=0.036), and having suffered emotional abuse during childhood (p=0.047) were associated with longer delay than 3 months between search for the first health professional and receiving the diagnosis of cancer (Table 3). Having the primary tumor located in the larynx (p=0.023), being female (p=0.017), drinking alcohol heavily (p=0.017), and low occurrence of childhood trauma (p=0.010) were associated with a longer time between noticing the first sign of the disease and receiving the definitive diagnosis of cancer (Table 3).

Multivariate analysis showed that the occurrence of physical abuse in childhood was an independent predictor for longer delay time for the cancer patient to seek attendance after noticing the first symptom (Table 4). These patients took longer than 3 months to seek care than patients without a history of physical abuse during childhood (OR=3.22, IC=1.020-10.183, p=0.046) (Table 4). HNC patients who had tumor located in the larynx and who had a history of childhood emotional abuse were more likely to have a delay time longer than 3 months between the first appointment by a health professional and receiving the diagnosis of cancer in relation to patients with oral cancer and patients without history of emotional abuse, respectively (OR=13.5, IC=2.645-69.355, p=0.002, OR=6.7, IC=1.974-23.293, p=0.002, respectively) (Table 4). HNC patients with tumors located in the larynx (OR=11.2, IC=2.204-56.987, p=0.004), and who were women (OR=5.6, IC=1.658-18.934, p=0.006), had a longer time delay between noticing the first symptom and having the diagnosis of the disease (Table 4). All analyzes were adjusted for gender, age, marital status, family income, and education. However, predictor variables remained in the model even after including these possible confounders.

Table 3. Associations between the different delay types and demographic, behavioral and clinicopathological variables and childhood trauma in HNC patients from univariate analysis.

Variables	Patient delay time€	Health system delay time€	Total delay time¥
Tumor location	.889	.065	.023*
Sex	.243	.506	.017*
CCI	.427	.030*	.894
Smoking	.329	.003*	.143
Alcohol intensity	.071	.184	.017*
Quartile CTQ	.653	.036*	.010*
Emotional Abuse	.442	.047*	.313
Physical Abuse	.030*	.444	.333

€considering up to 3 months and more than 3 months; ¥considering up to 6 months and more than 6 months
*Values are considered statistically significant at p<0.05 (Chi Square Test or Fisher's exact tests).
Abbreviation: CCI, charlson comorbidity index. CTQ, Childhood Trauma Questionnaire.

Table 4. Logistic regression analysis considering CTQ measures and demographic and clinicopathological variables as independent for the delay time of the HNC patients.

Dependent Variables	*Independent Variables*	*OR*	*95% CI*	*P value**	*OR adjusted$^{\alpha}$*	*95% CI*	*P value**
Patient delay time€	Physical abuse	3.2	1.020-10.183	0.046	3.2	0.981-10.743	0.049
Health system delay time€	Tumor location	13.5	2.645-69.355	0.002	7.5	1.658-34.810	0.009
	Emotional abuse	6.7	1.974-23.293	0.002	3.1	1.188-8,177	0.021
Total delay time¥	Tumor location	11.2	2.204-56.987	0.004	13	2.223-77.013	0.004
	Sex	5.6	1.658-18.934	0.006	3.9	1.176-13.061	0.026

€considering up to 3 months and more than 3 months; ¥considering up to 6 months and more than 6 months
*Values are considered statistically significant at p<0.05. Abbreviation: CTQ, Childhood Trauma Questionnaire; $^{\alpha}$OR adjusted for gender, age, marital status, income and education.

4 DISCUSSION

Our results show significant delays for HNC patients to seek care after noticing the first sign of the disease (average of 129.50 days), as well as the health system to notify the diagnosis of cancer after the patient's first consultation (average of 196.43 days). Consequently, the mean total time between the first perception of the disease and receiving the diagnosis was considerably long (average of 326.08 days). In patients with colorectal cancer, Wu et al. found that the mean patient delay was also high (more than 120 days).[21] A recent study which was held in London showed that the average time delay for HNC patients was more than 90 days, while the patient's path in the health system to the definitive diagnosis was 300 days.[22] Regardless of the type of tumor, this patient's delay observed in our and other studies lead to a high chance of cancer being diagnosed at an advanced stage, delaying treatment initiation and drastically reducing the chances of a cure[22,23] The main factors associated with patient delay in cancer diagnosis are the socioeconomic status and low education.[22] However, in our study we revealed for the first time that traumatic experiences lived in childhood were strongly associated with the three different delay types evaluated (patient time, health system time and total time). Childhood trauma has been pointed out as a relevant predictor for high levels of psychological symptoms, cancer-related fatigue, poorer well-being, and increased levels of inflammatory markers associated with poorer disease prognosis.[12,24-26] However, for the first time, evidence is brought revealing that the delay in the diagnosis of cancer may be directly related to the occurrence of traumatic experiences in childhood.

Using a sample of patients with HNC as an exploratory model, our findings reveal that physical abuse experienced in childhood was a risk factor for the patient to take more than 90 days to seek a health service after noticing the first sign of the disease. Physical abuse is a subtype of trauma characterized by the use of physical force against the child, which can lead to damage to physical and emotional development[27] Individuals who had a history of childhood physical abuse had a 49% chance of getting cancer at some moment in their lives.[28] Women who were physically abused in childhood were 96% more likely to be diagnosed with cervical cancer than women without abuse.[29] In our study, patients who reported experiencing physical aggression and violence during childhood, were 3.22 times more likely to take longer to seek care than patients without a history of this trauma subtype. It is not easy to

identify the mechanisms behind this association that is now emerging. However, we hypothesize that in these individuals who were traumatized at an early stage of life, touching certain body areas can produce sensations that remind them of the abusive or traumatic touch experienced in childhood. Thus, these patients would have greater resistance to being submitted to a physical examination or even to trigger a marked fear of having a diagnosis of a disease that would place them under the need to receive greater care in relation to physical health. Individuals who have suffered childhood trauma display an increased tendency towards fear than non-traumatized individuals[30] Experiencing physical abuse as a child can have serious and long-term consequences, such as the development of the risk behaviors smoking and alcoholism, mental disorders and chronic diseases.[12,31] That is, having a history of this trauma subtype not only influences the individual to come into contact with substances associated with the development of HNC (especially smoking and alcoholism), as also induces the patient to take longer to seek clinical care after noticing the lesion.

Regarding the health system delay time, our results also showed for the first time that patients who had a history of childhood emotional abuse had longer delay of the health system to receive a cancer diagnosis after seeking for the first health service. As this is an unprecedented finding, we may only, for the moment, speculate on some explanation. We consider that cancer patients who had a hostile environment in childhood, being constantly despised and threatened by the caregivers (individuals who should care and provide protection), would be more likely to present deficits in social interaction, disfavoring attitudes and behaviors necessary for their communication in different health services. One study showed that social interaction was affected in borderline personality disorder patients who had a history of childhood emotional abuse.[32] Larynx cancer patients had longer delay of the health system for receiving a cancer diagnosis after seeking for the first health service (OR=13.5, IC=2.645-69.355, p=0.002) and longer total time, comprised between the first perception of the disease and being diagnosed with cancer (OR=11.2, IC=2.204-56.987, p=0.004). We consider that this time was significantly longer in patients with larynx cancer compared to those with tumors in oral cavity and oropharynx due to frequent symptom interpretation problems or due to deficient initial examination by the health professional. In the study by Teppo & Alho, 2009 the survival and tumor

size of larynx cancer patient were affected by the healthcare professional's delay in diagnosing the disease (more than six months after the first appointment).[33] The authors also consider that the delay may be due to the professional's attitudes towards the common symptoms of these cancer patients, like hoarseness, for example.[33]

The results of the current study also revealed that women with cancer had a longer total delay time (time between the first perception of the disease and being diagnosed with cancer) compared to men. A possible justification for this result may be based on the cultural characteristics inherent to the female sex, for example, taking care of the house, the family, the job, leaving for later the care of your own health. In general, women considerably influence the spouse to constantly seek medical care, however, the man does not influence the partner to seek medical help.[32,33] Moreover, women receive less support from their partners when they are diagnosed with cancer.[33] Unfortunately, the quality of marital relationships was not addressed in the current study. In addition, compared to men, female patients with HNC tend to have fewer classic risk factors for cancer (smoking and alcoholism). Due to the absence of a classic clinical profile for the disease, there could be greater difficulty, and therefore more time, for some health professionals to conclude the definitive diagnosis.[34] This study has some limitations. The information regarding patient and health system delay times depended exclusively on the patients' memory. This memory can be impaired by the age of the patient (most of them were over 50 years old). While the trajectory time in the health system can be measured in a relatively accurate way, the patient delay until seeking care may be more difficult to measure accurately. The date of onset of symptoms is based only in the patient's own perception, which is subjective and may be influenced by social and cultural factors.[35] Other limitations were the categorization of the CTQ measures and delay time, so that only one cutoff point (3 months) was used. Finally, the assessment and measurement of childhood trauma was performed only by a validated questionnaire. Although the method used to assess childhood trauma is the most used worldwide, the patient may not feel comfortable reporting painful childhood events, denying the occurrence of the event, or not having their memory of the event.

Overall, the current study reveals for the first time that together with other clinicopathological factors, the occurrence of traumatic experiences in childhood can

be predictive for the delay of the patient with head and neck cancer to seek health services and receive a diagnosis. Although this relationship needs to be explored in patient samples from different countries and cultures, as well as with other types of malignant tumors, our findings can help to propose new strategies for secondary cancer prevention. They suggest that public health policies for reducing the delay in cancer detection should also be directed towards focusing on the earlier stages of life. The new evidence presented here may stimulate that the secondary cancer prevention policies aiming at its early detection should consider the consequences of childhood trauma and the development of strategies for its mitigation.

REFERENCES

1. Kumar A, Bhagabaty SM, Tripathy JP, Selvaraj K, Purkayastha J, Singh R. Delays in diagnosis and treatment of breast cancer and the pathways of care: a mixed methods study from a tertiary cancer centre in north east India. Asian Pac J Cancer Prev 2019;20:3711-21.

2. Ganesan S, Sivagnanganesan S, Thulasingam M, et al. Diagnostic delay for head and neck cancer in South India: a mixed-methods study. Asian Pac J Cancer Prev 2020;21:1673-8.

3. Chiou SJ, Lin W, Hsieh CJ. Assessment of duration until initial treatment and its determining factors among newly diagnosed oral cancer patients: a population-based retrospective cohort study. Medicine 2016;95:e5632.

4. Lee SC, Tang IP, Avatar SP, et al. Head and neck cancer: possible causes for delay in diagnosis and treatment. Med J Malaysia 2011;66:101-4.

5. World Health Organization (WHO). Guide to cancer early diagnosis. Geneva: Switzerland; 2017.

6. Noonan B. Understanding the reasons why patients delay seeking treatment for oral cancer symptoms from a primary health care professional: an integrative literature review. Eur J Oncol Nurs 2014;18:118-24.

7. Sawicki M, Szczyrek M, Krawczyk P, Rybojad P, Jabłonka A, Milanowski J. Reasons for delay in diagnosis and treatment of lung cancer among patients in Lublin Voivodeship who were consulted in Thoracic Surgery Department. Ann Agric Environ Med 2013;20:72-6.

8. Roberts SJ, Chandler GE, Kalmakis K. A model for trauma-informed primary care. J Am Assoc Nurse Pract. 2019;31:139-44.

9. Gilgoff R, Singh L, Koita K, Gentile B, Marques SS. Adverse childhood experiences, outcomes, and interventions. Pediatr Clin North Am 2020;67:259-73.

10. Han TJ, Felger JC, Lee A, Mister D, Miller AH, Torres MA. Association of childhood trauma with fatigue, depression, stress, and inflammation in breast cancer patients undergoing radiotherapy. *Psychooncology* 2016;25:187-93.

11. Archer JA, Hutchison IL, Dorudi S, Stansfeld SA, Korszun A. Interrelationship of depression, stress and inflammation in cancer patients: a preliminary study. *J Affect Disord* 2012;143:39-46.

12. Sarafim-Silva BAM, Duarte GD, Sundefeld MLMM, Biasoli ÉR, Miyahara GI, Bernabé DG. Childhood trauma is predictive for clinical staging, alcohol consumption, and emotional symptoms in patients with head and neck cancer. Cancer 2018;124:3684-92.

13. Witek Janusek L, Tell D, Albuquerque K, Mathews HL. Childhood adversity increases vulnerability for behavioral symptoms and immune dysregulation in women with breast cancer. *Brain Behav Immun* 2013;30:S149-62.

14. Brown DW, Anda RF, Felitti VJ, et al. Adverse childhood experiences are associated with the risk of lung cancer: a prospective cohort study. *BMC Public Health*. 201019;10:20.

15. Yane K. I. Current Status and Perspective of AJCC/UICC TNM Classification System. Gan To Kagaku Ryoho 2018;45:1042-5.

16. Charlson M, Pompei P, Ales K, MacKenzie C. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.

17. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: myths, truths and clinical relevance. Scand J Pain 2016;13:67-75.

18. Schwantes-An TH, Zhang J, Chen LS, et al. Association of the OPRM1 variant rs1799971 (A118G) with non-specific liability to substance dependence in a collaborative de novo meta-analysis of european-ancestry cohorts. Behav Genet 2016;46:151-69.

19. Bernstein D, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry* 1994;151:1132-6.

20. Grassi-Oliveira R, Stein LM, Pezzi JC. Translation and content validation of the Childhood Trauma Questionnaire into Portuguese language. *Rev Saude Publica* 2006;40:249-55.

21. Wu XD, Zeng YY, Wu XJ, Qin HY. The prevalence and correlates of prehospital delay and health belief in chinese patients with colorectal cancer. Gastroenterol Nurs 2020;43:186-95.

22. Kassirian S, Dzioba A, Hamel S, et al. Delay in diagnosis of patients with head-and-neck cancer in Canada: impact of patient and provider delay. Curr Oncol 2020;27:e467-77.

23. Unger-Saldaña K, Miranda A, Zarco-Espinosa G, Mainero-Ratchelous F, Bargalló-Rocha E, Miguel Lázaro-León J. Health system delay and its effect on clinical stage of breast cancer: Multicenter study. Cancer 2015;121:2198-206.

24. Bower JE, Crosswell AD, Slavich GM. Childhood adversity and cumulative life stress: risk factors for cancer-related fatigue. *Clin Psychol Sci* 2014;2:108-15.

25. Fagundes CP, Lindgren ME, Shapiro CL, Kiecolt-Glaser JK. Child maltreatment and breast cancer survivors: social support makes a difference for quality of life, fatigue and cancer stress. *Eur J Cancer* 2012;48:728-36.

26. Crosswell AD, Bower JE, Ganz PA. Childhood adversity and inflammation in breast cancer survivors. Psychosom Med. 2014; 76:208-214.

27. Norman RE, Byambaa M, De R, Butchart A, Scott J, Vos T. The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. PLOS MED 2012;9:e1001349.

28. Fuller-Thomson E, Brennenstuhl S. Making a link between childhood physical abuse and cancer: results from a regional representative survey. Cancer 2009;115:3341-50.

29. Hindin P, Btoush R, Carmody DP. History of childhood abuse and risk for cervical cancer among women in low-income areas. J Womens Health 2019;28:23-29.

30. Suzuki A, Poon L, Kumari V, Cleare AJ. Fear biases in emotional face processing following childhood trauma as a marker of resilience and vulnerability to depression. Child Maltreat. 2015;20:240-50.

31. Felitti VJ, Anda RF, Nordenberg D, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the Adverse Childhood Experiences (ACE) study. Am J Prev Med 2019;56:774-86.

32. Grave U, Glanert S, Borchfeld K, et al. Differential effect of childhood emotional abuse on present social support in borderline disorder and depression: a cross-sectional study. Eur J Psychotraumatol 2021;12:1968612.

33. Teppo H, Alho OP. Comorbidity and diagnostic delay in cancer of the larynx, tongue and pharynx. Oral Oncol 2009;45:692-5.

34. Wilsnack RW, Wilsnack SC, Gmel G, Kantor LW. Gender differences in binge drinking. Alcohol Res 2018;39:57-76.

35. Pedersen AF, Olesen F, Hansen RP, Zachariae R, Vedsted P. Social support, gender and patient delay. Br J Cancer 2011;104:1249-55.

ANEXOS

ANEXO A – Comitê de Ética em Pesquisa

UNESP - FACULDADE DE ODONTOLOGIA-CAMPUS DE ARAÇATUBA/ UNIVERSIDADE

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Análise da associação entre os fatores psicológicos e fisiológicos em pacientes com câncer de cabeça e pescoço.

Pesquisador: DANIEL GALERA BERNABÉ

Área Temática:

Versão: 1

CAAE: 55521416.4.0000.5420

Instituição Proponente: Universidade Estadual Paulista Júlio de Mesquita Filho

Patrocinador Principal: Universidade Estadual Paulista Júlio de Mesquita Filho
Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.521.786

Apresentação do Projeto:

Recentes estudos mostram que desordens emocionais em pacientes com câncer de mama podem estar correlacionadas a eventos traumáticos vivenciados na infância. Embora pacientes com câncer de cabeça e pescoço apresentem altos níveis de ansiedade, depressão e variações de humor, pouco é conhecido sobre os fatores predisponentes para estas desordens, bem como para a manutenção dos comportamentos de tabagismo e alcoolismo após o diagnóstico e tratamento da doença. O objetivo do presente estudo é avaliar a influência dos eventos traumáticos na infância sobre as desordens emocionais, os comportamentos de tabagismo e alcoolismo e os níveis de hormônios relacionados ao estresse em pacientes com câncer de cabeça e pescoço.

Objetivo da Pesquisa:

Avaliar a influência dos eventos traumáticos na infância sobre as desordens emocionais, os comportamentos de tabagismo e alcoolismo e os níveis de hormônios relacionados ao estresse em pacientes com câncer de cabeça e pescoço.

Avaliação dos Riscos e Benefícios:

Riscos:

Endereço: JOSE BONIFACIO 1193
Bairro: VILA MENDONCA **CEP:** 16.015-050
UF: SP **Município:** ARACATUBA
Telefone: (18)3636-3200 **Fax:** (18)3636-3332 **E-mail:** andrebertoz@foa.unesp.br

Este estudo oferece riscos mínimos aos seus participantes, pois suas metodologias são: coletas de sangue e saliva cujas técnicas são amplamente conhecidas e aplicadas em laboratórios de diagnóstico. Neste estudo a coleta de sangue será realizada por um profissional especializado da área de enfermagem. Os testes psicológicos que serão utilizados são reconhecidos mundialmente e validados na população brasileira e estes serão aplicados por um profissional da área de psicologia.

Benefícios:
As avaliações dos questionários psicológicos serão realizadas por um profissional da área de psicologia que oferecerá suporte psicológico ao paciente caso aja necessidade. A pesquisa favorece o processo de percepção de fatores inconscientes que possam influenciar no modo de viver do indivíduo e de como estes fatores podem interferir na própria doença. Além disso, será oferecido aos grupos controles uma avaliação clínica intraoral com o objetivo de detectar lesões bucais, com isso favorecendo o diagnóstico precoce de possíveis lesões benignas e malignas.

Comentários e Considerações sobre a Pesquisa:
A pesquisa apresenta-se bem estruturada e com objetivos bem definidos.

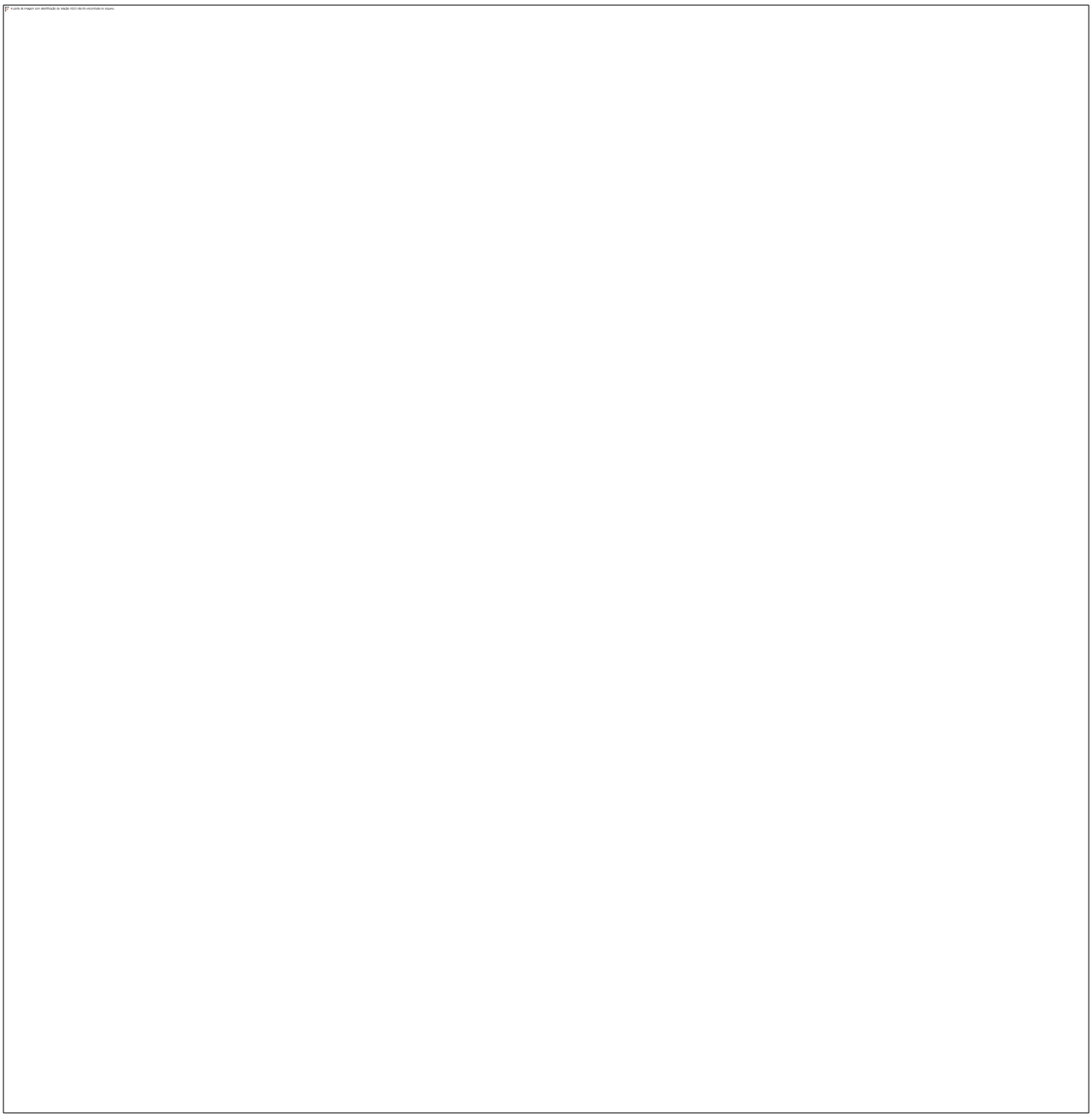
Considerações sobre os Termos de apresentação obrigatória:
Há necessidade de adequações.

Recomendações:
Conferir o nome do projeto na folha de rosto e demais documentos, visto que deve constar o mesmo nome em todos os documentos apresentados.

Atualizar o cronograma de execução nas informações básicas do projeto, devendo este estar igual em todos os documentos e considerando, ainda, que nenhum protocolo em andamento será autorizado pelo CEP/CONEP.

Conclusões ou Pendências e Lista de Inadequações:
O CEP solicita que sejam tomadas as providências cabíveis para sanar as pendencias apresentadas.

Considerações Finais a critério do CEP:
Informamos ao(a) senhor(a) pesquisador(a) que o prazo máximo para o atendimento das pendências será de 30 dias corridos a partir da emissão deste pareoer. Caso o prazo não seja respeitado e/ou as pendências atendidas a contento, o protocolo será retirado do sistema. No


A parte da imagem com identificação da relação rId13 não foi encontrada no volume.

ANEXO B - Normas para publicação no periódico *New England Journal of Medicine* (NEJM)

Journal: *New England Journal of Medicine* (NEJM)

https://www.nejm.org/author-center/new-manuscripts